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Bevacizumab Combined With Oxaliplatin-Based Chemotherapy Prolongs Survival for Previously Treated Patients With Advanced Colorectal Cancer

Preliminary results from a large, randomized clinical trial for patients with advanced colorectal cancer who had previously received treatment show that those who received bevacizumab (Avastin™) in combination with an oxaliplatin (Eloxatin™) regimen known as FOLFOX4 lived longer than patients who received FOLFOX4 alone.

The Data Monitoring Committee overseeing the trial (known as E3200)* recommended that the results of a recent interim analysis be made public because the study had met its primary endpoint of demonstrating improved overall survival. Researchers found that the patients in the trial who received bevacizumab in combination with FOLFOX4 (a regimen of oxaliplatin, 5-fluorouracil and leucovorin) had a median overall survival of 12.5 months compared to patients treated with FOLFOX4 alone, who had a median overall survival of 10.7 months. This difference is statistically significant and corresponds to a 17 percent improvement in median overall survival. There was a 26 percent reduction in the risk of death (hazard ratio of 0.74) for patients in this study who received bevacizumab plus FOLFOX4 compared to those who received FOLFOX4 alone.

The clinical trial was sponsored by the National Cancer Institute (NCI), part of the National Institutes of Health, and conducted by a network of researchers led by the Eastern Cooperative Oncology Group. Genentech, Inc., which manufactures bevacizumab, provided bevacizumab for the trial under the Cooperative Research and Development Agreement

* E3200: Phase III Trial of Bevacizumab, Oxaliplatin, Fluorouracil and Leucovorin Versus Oxaliplatin, Fluorouracil and Leucovorin Versus Bevacizumab Alone in Previously Treated Patients With Advanced Colorectal Cancer

(CRADA) with NCI for the clinical development of bevacizumab. Sanofi-Synthelabo, a member of the Sanofi-Aventis Group and manufacturer of oxaliplatin, provided that drug for the trial under its CRADA with NCI.

"These results are simply more good news for people with colorectal cancer," said Study Chair Bruce J. Giantonio, M.D., of the University of Pennsylvania's Abramson Cancer Center in Philadelphia. "We now know that bevacizumab added to second-line chemotherapy with FOLFOX4 improves survival. With these findings, we can now more confidently expect survival for people with advanced disease to be more than double what it was just a few years ago." According to Giantonio, preliminary results of the E3200 trial will be presented at the ASCO Gastrointestinal Cancers Symposium to be held in Hollywood, Fla., on Jan.27-29, 2005.

"This trial highlights benefits of the public-private collaborations that NCI has spearheaded over the last several years," said James H. Doroshow, M.D., director of NCI's Division of Cancer Treatment and Diagnosis and leader of NCI's Clinical Trials Working Group. "Working with the biotechnology and pharmaceutical companies, NCI was able to coordinate the drug development of these two new agents (bevacizumab and oxaliplatin) in combination and, through the dedication and commitment of the patients and physicians who participated in the study, provide an important advance for patients."

A total of 829 patients were enrolled in the study between October 2001 and April 2003. Patients previously had received a fluorouracil-based therapy and irinotecan (Camptosar™), either alone or at the same time, for advanced disease or if their disease had relapsed within six months of concluding adjuvant (post-surgical) treatment with these chemotherapy agents. Patients were randomized to one of three treatment groups. One patient group received the standard FOLFOX4 treatment plus bevacizumab. The second group received the standard FOLFOX4 treatment only, and the third group received bevacizumab alone. In March 2003, the study investigators suspended randomization to the third treatment arm, bevacizumab alone, on the recommendation of the Data Monitoring Committee when review of early results suggested that overall survival for patients in that group might be lower than that of patients treated in the other two groups.

Treatment toxicities observed in this study were consistent with those side effects observed in other clinical trials in which bevacizumab was combined with chemotherapy. Side effects included neuropathy (problems with nerve function) for FOLFOX4 and high blood pressure and bleeding for bevacizumab.

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Bevacizumab is designed to bind to and inhibit Vascular Endothelial Growth Factor (VEGF), a protein that plays a critical role in tumor angiogenesis, the formation of new blood vessels to the tumor. Oxaliplatin is a novel platinum-based anticancer drug that destroys cancer cells.

“The results of this study are very important for all those living with advanced colorectal cancer,” said NCI Director Andrew C. von Eschenbach, M.D. “They provide further confirmation that a biologic agent that targets a tumor’s blood supply can prolong survival when combined with chemotherapy, even for patients who have previously received therapy for advanced disease.”

An estimated 106,370 people will be diagnosed with colon cancer and an estimated 40,570 people will be diagnosed with rectal cancer in the United States in 2004. Colorectal cancer is the third most commonly diagnosed cancer in this country both in men and in women. An estimated 56,730 deaths from colorectal cancer will occur in 2004 in the United States, accounting for about 10 percent of all cancer deaths in the nation.

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